Prognosis of sporadic resected small (<= 2 cm) nonfunctional pancreatic neuroendocrine tumors - a multi-institutional study

Pancreas 2000 res grp

2018-03

Pancreas 2000 res grp 2018 , ' Prognosis of sporadic resected small (<= 2 cm) nonfunctional pancreatic neuroendocrine tumors - a multi-institutional study ' , HPB , vol. 20 , no. 3 , pp. 251-259 . https://doi.org/10.1016/j.hpb.2017.08.034

http://hdl.handle.net/10138/233966
https://doi.org/10.1016/j.hpb.2017.08.034

ORIGINAL ARTICLE

Prognosis of sporadic resected small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors – a multi-institutional study

Ville J. Sallinen[1,2], Tessa T.Y. Le Large[3], Elke Tieftrunk[4], Shamil Galeev[5], Zahar Kovalenko[6], Sven-Petter Haugvik[7,8], Anne Antila[9], Oskar Franklin[10], Emma Martinez-Moneo[11], Stuart M. Robinson[12], Francesco Panzuto[13], Nicolas Regenet[14], Francesca Muffatti[15], Stefano Partelli[15], Dominik Wiese[16], Philippe Ruszniewski[17,18], Bertrand Dousset[19,20], Bjørn Edwin[7,21,22], Detlef K. Bartsch[16], Alain Sauvanet[18,23], Falconi Massimo[15], Güralp O. Ceyhan[4], Sebastien Gaujoux[19,20] & on the behalf of the Pancreas 2000 research group

[1]Department of Abdominal Surgery, [2]Department of Transplantation and Liver Surgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland, [3]Department of Surgery, VU University Medical Center, Amsterdam, The Netherlands, [4]Department of Surgery, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany, [5]General Surgery Department, Saint Luke's Clinical Hospital, Saint Petersburg, [6]Federal Medical and Rehabilitation Center, Department of Surgical Oncology, Moscow, Russia, [7]The Intervention Center, Oslo University Hospital, Oslo, [8]Department of Surgery, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway, [9]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland, [10]Department of Surgical and Perioperative Sciences, Umea University, Umea, Sweden, [11]Gastroenterology Department, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain, [12]Department of HPB Surgery, Freeman Hospital, Newcastle Upon Tyne, UK, [13]Digestive and Liver Disease Unit, Sant'Andrea Hospital – Sapienza University of Rome, Italy, [14]Department of Digestive and Endocrine Surgery, Institut des Maladies Digestives (IMAD), Nantes 44093, France, [15]Chirurgia Del Pancreas, Chirurgia Del Pancreas, Pancreas Translational & Clinical Research Center, Università Vita e Salute, Ospedale San Raffaele IRCC, Milano, Italy, [16]Department of Visceral, Thoracic and Vascular Surgery, Philipps University Marburg, Marburg, Germany, [17]Department of Gastroenterology, Pôle des Maladies de L'Appareil Digestif (PMAD), DHU Unity, Clichy 92110, [18]Université Paris Diderot, [19]Department of Digestive, Pancreatic and Endocrine Surgery, Cochin Hospital, APHP, [20]Faculté de Médecine Paris Descartes, Université Paris Descartes, Sorbonne Paris Cité, Paris, France, [21]Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, [22]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, and [23]AP-HP, Hôpital Beaujon, Department of Hepato-Pancreato-Biliary Surgery, Pôle des Maladies de L'Appareil Digestif (PMAD), DHU Unity, University Paris VII, AP-HP, Hôpital Beaujon, Clichy 92110, France

Abstract

Background: Malignant potential of small (≤20 mm) nonfunctional pancreatic neuroendocrine tumors (sNF-PNET) is difficult to predict and management remain controversial. The aim of this study was to assess the prognosis of sporadic nonmetastatic sNF-PNETs.

Methods: Patients were identified from databases of 16 centers. Outcomes and risk factors for recurrence were identified by uni- and multivariate analyses.

Results: sNF-PNET was resected in 210 patients, and 66% (n = 138) were asymptomatic. Median age was 60 years, median tumor size was 15 mm, parenchyma-sparing surgery was performed in 42%. Postoperative mortality was 0.5% (n = 1), severe morbidity rate was 14.3% (n = 30), and 14 of 132 patients (10.6%) with harvested lymph nodes had metastatic lymph nodes. Tumor size, presence of biliary or pancreatic duct dilatation, and WHO grade 2–3 were independently associated with recurrence. Patients with tumors sized ≤10 mm were disease free at last follow-up. The 1-, 3- and 5-year disease-free survival rates for patients with tumors sized 11–20 mm on preoperative imaging were 95.1%, 91.0%, and 87.3%, respectively.

Conclusions: In sNF-PNETs, the presence of biliary or pancreatic duct dilatation or WHO grade 2–3 advocate for surgical treatment. In the remaining patients, a wait-and-see policy might be considered.

Received 7 February 2017; accepted 30 August 2017

Correspondence

Ville J. Sallinen, Department of Abdominal Surgery, Helsinki University Hospital, Haartmaninkatu 4, 00029 HUS, Helsinki, Finland. E-mail: ville.salinen@helsinki.fi

This paper was presented at 12th Biennial E-AHPBA Congress 2017, Mainz, Germany held 23th–26th May, 2017.

Introduction

Pancreatic neuroendocrine neoplasms are rare and heterogeneous neoplasms with variable malignant potential.[1,2] With the widespread use of cross-sectional imaging, asymptomatic nonfunctional pancreatic neuroendocrine tumors are now diagnosed with increasing frequency.[3] Surgical resection is the only potential cure for these tumors, and has long been advocated for all lesions. However, since pancreatic surgery carries a high risk of morbidity and mortality,[4–7] the benefit/risk balance need to be carefully weighted. Small (≤2 cm) sporadic nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) have been suggested as good candidates for surveillance.[8–11] However, all surgical series agree that about 10–15% of small NF-PNETs have malignant potential with lymph node metastasis on pathologic specimens or later recurrence.[12–15] It is unclear how to preoperatively predict malignant behavior of small NF-PNETs and how to select patients for surgery or a surveillance strategy.

The aim of this European multicentric study was to assess postoperative outcome and risk factors for recurrence of resected sporadic small (≤20 mm) NF-PNETs.

Methods

Inclusion criteria and data collection

Patients undergoing surgery between 1999 and 2014 were identified from pancreatic surgical databases of 16 European participating centers. Inclusion criterias were patients with (i) histopathologically proven pancreatic neuroendocrine tumors (PNET), (ii) nonfunctional tumor as defined by the ENETS guideline (nonfunctional status defined by the absence of a hormone hypersecretion syndrome[16]), (iii) with largest diameter of 20 mm or below on preoperative cross-sectional imaging and (iv) completely resected (i.e. R0/R1) (by pancreas sparing or standard resection). Exclusion criterias were (i) recurrence of preoperatively resected PNET, (ii) PNET presenting with synchronous metastasis, (iii) PNET from proven genetic origin (Multiple Endocrine Neoplasia type 1, Von Hippel Lindau Disease), (iv) PNET with macroscopically incomplete (R2) resection and (v) duodenal/ampullary neuroendocrine tumors. Demographic, radiographic, pathologic, postoperative, and follow-up data were obtained from each center's databases with additional retrospective medical record review performed when necessary. Data were recorded in a preformatted data collection sheet. Minimum preoperative work-up included at least an abdominal computed tomography scan before surgery, magnetic resonance imaging, endoscopic ultrasonography and/or somatostatin receptor imaging, depending on the clinical situation and according to each attending discretion.

Postoperative course and follow-up

Postoperative mortality included all deaths occurring before hospital discharge or within 90-days. Morbidity included all complications following surgery until discharge and/or readmission, and was graded according to the Clavien-Dindo classification.[17] Postoperative pancreatic fistula was defined according to the International Study Group of Pancreatic Surgery (ISGPS).[18] Follow-up was based on clinical, radiological, and laboratory assessments, and updated on outpatient evaluation, routine postoperative visits, and/or correspondence. Pancreatic lesions were graded according to the 2010 World Health Organization classification.[19] Follow-up information was available for all patients.

Statistical analyses

Values are expressed as median (interquartile), or percentage, as appropriate. Fisher exact test was used to compare differences in discrete or categorical variables, the Mann–Whitney *U*-test for continuous variables and the Wilcoxon rank-sum test was used for paired continuous variables. Disease-free survival (DFS) (time from surgery to time of first radiological evidence of local, regional, or distant relapse, or death due to any cause) and overall survival (time from surgery until death, regardless of cause) were estimated by the method of Kaplan–Meier, and the log-rank test was used to compare survival curves. The Hazard ratio (HR) and its 95% confidence interval (CI) were estimated using Cox's proportional hazards regression model in a uni- and multivariate analysis. Patients were censored as of their last follow-up visit if they were alive and/or disease-free throughout the study period. All tests were two-sided. For all tests, statistical significance was defined by $p < 0.05$. Data were analyzed with SPSS 21 (IBM, Armonk, USA).

Results

Patients and tumors characteristics

Overall, 210 patients fulfilling the inclusion criteria were eligible and included in the analyses. Patient characteristics are shown in Table 1. Although all patients had presumed sporadic tumors, five patients (2.4%) had multiple lesions.

Surgical procedure and postoperative course

Formal resection (pancreaticoduodenectomy or distal pancreatectomy) was performed in 121 patients and the remaining 89 underwent parenchyma-sparing surgery (enucleation or central pancreatectomy) (Table 2). Major complication (Clavien-Dindo grade ≥ 3) occurred in 31 patients and the fistula rate was 40.5% ($n = 85$), including clinically relevant (grade B or C) in 16.7% ($n = 35$). The 90-day postoperative mortality rate was 0.5% ($n = 1$). Risk for postoperative pancreatic fistula was greatest in parenchyma-sparing surgery but no differences regarding mortality, overall complications, delayed gastric emptying, or postoperative hemorrhage were observed (Table 3).

Tumor pathology

The median tumor size on pathological examination was 15 mm and significantly different ($p = 0.04$) from the one measure on preoperative imaging (Table 2). The median size discrepancy compared to preoperative radiological evaluation was 2 (1–5)

Table 1 Basic characteristics of the 210 included patients with nonfunctional pancreatic neuroendocrine tumors

Variable	Median (IQR) or percentage (*n*)
Age (years)	60 (55–68)
Male	45% (95)
Symptoms	
None	65.7% (138)
Pain	20.9% (44)
Jaundice	3.8% (8)
Pancreatitis	2.4% (5)
Weight loss	3.3% (7)
Nonspecific	3.3% (7)
Preoperative radiological tumor characteristics	
Size on cross-sectional imaging (mm)	15 (11–19)
Location	
Head	30% (63)
Body	38.6% (81)
Tail	31.4% (66)
Multiple lesions	2.4% (5)
Suspicion of nodal involvement[a]	3.8% (6)

[a] On 156 patients with available data.

Table 2 Surgical procedure, postoperative course and pathological characteristics of nonfunctional pancreatic neuroendocrine tumors

Variable	Median (IQR) or percentage (*n*)
Type of surgery	
Pancreaticoduodenectomy	12.8% (27)
Median pancreatectomy	9% (19)
Distal pancreatectomy	44.8% (94)
Enucleation	33.3% (70)
Complications	
Clavien-Dindo 1-2	41.3% (85)
Clavien-Dindo 3	12.6% (26)
Clavien-Dindo 4	1.9% (4)
Clavien-Dindo 5	0.5% (1)
Length of hospital stay[a] (days)	9 (6–13)
Size on pathology (mm)	15 (10–18)
WHO 2010 grade	
Grade 1	81% (162)
Grade 2	18.5% (37)
Grade 3	0.5% (1)
Lymph nodes	
Patients with examined lymph nodes on specimen	62.9% (132)
Lymph nodes examined/patient	6 (3–14)
Patients with positive lymph node on pathology	10.6% (14)

WHO – World Health Organization.
[a] On 157 patients with available data.

mm. In 6.1% ($n = 13$) of cases, the size of the tumors were more than 5 mm smaller in the pathological analysis, while 10.5% tumors ($n = 22$) were more than 5 mm larger in the pathological analysis compared to preoperative cross-sectional imaging. While the radiological measurement was $\leq$20 mm in all tumors, 9.6% ($n = 20$) of the tumors were larger than 20 mm in the pathological analysis.

In almost two thirds of patients (62.9%; $n = 132$), lymph nodes were present and analyzed with the specimen. When present, a median of six nodes (3–14) were analyzed. In patients with lymphadenectomy, 10.2% (14 out of 132 patient with lymphadenectomy) had metastatic lymph nodes. The corresponding rates of metastatic lymph nodes were 23% (6 patients with metastatic lymph nodes/26 patients with harvested lymph nodes/27 patient total) for pancreaticoduodenectomy, 4% (3/69/94) for distal pancreatectomy, 31% (4/13/19) for central pancreatectomy, and 4% (1/24/70) enucleation. 3% ($n = 4$) of WHO 2010 grade 1, 16% ($n = 6$) of grade 2, and 100% ($n = 1$) of grade 3 tumors had metastatic lymph nodes. An R1 resection was considered to have been performed in 23 (11%) of tumors, all but three of these following parenchyma-sparing surgery.

Long-term outcome

After a median follow-up of 36 months (16–64), the median disease-free survival was not reached, and the 1-, 3- and 5-year disease-free survival rates were 96.4% (±1.3%), 93.5% (±1.9%), 93.5% (±1.9%), respectively (Fig. 1a). Overall 5.9% ($n = 11$) of patients developed tumor recurrence at a median time of 8 (6–28) months. The most common site of recurrence was liver ($n = 5$), followed by lymph nodes ($n = 2$) and lung ($n = 2$). There was one local recurrence and one recurrence in multiple sites. Four of the 11 patients (36%) with recurrence underwent metastasectomy, of whom two (50%) remained free of disease during the follow-up. Disease-free survival was similar in patients who underwent pancreas-sparing pancreatectomy compared to formal resection (Fig. 2).

The median overall survival was not reached, and the 1-, 3- and 5-year overall survival rates were 99.0% (±0.7%), 97.5% (±1.3%), and 96.2% (±1.8%) respectively. Only one patient, with a grade 3 tumor, died of metastatic PNET during follow-up. The cause of death was unrelated to PNET in three patients, and unknown in one patient.

Results of the univariate and multivariate Cox proportional hazards models are shown in Table 4 for both preoperative and postoperative parameters. Tumor size, and the presence of biliary or pancreatic duct dilatation on preoperative computed tomography (CT) were independent predictors of recurrence on

Table 3 Complications by the type of operation in 210 patients with nonfunctional pancreatic neuroendocrine tumors

	Pancreaticoduodenectomy, $n = 27$	Distal pancreatectomy, $n = 94$	Median pancreatectomy, $n = 19$	Enucleation, $n = 70$	p
Pancreatic fistula					
Grade A	2 (7%)	17 (18%)	6 (32%)	25 (36%)	0.006
Grade B	2 (7%)	11 (12%)	3 (16%)	7 (10%)	
Grade C	2 (7%)	3 (3%)	0	7 (10%)	
Total	6 (22%)	31 (33%)	9 (47%)	39 (56%)	
Hemorrhage					
Grade A	0	1 (1%)	0	4 (6%)	0.18
Grade B	2 (7%)	1 (1%)	0	1 (1%)	
Grade C	1 (4%)	1 (1%)	1 (5%)	2 (3%)	
Total	3 (11%)	3 (3%)	1 (5%)	7 (10%)	
Delayed gastric emptying					
Grade A	1 (4%)	3 (3%)	1 (5%)	3 (4%)	0.30
Grade B	2 (7%)	0	0	1 (1%)	
Grade C	0	0	0	1 (1%)	
Total	3 (11%)	3 (3%)	1 (5%)	5 (7%)	
Clavien-Dindo ≥ 3	3 (11%)	10 (11%)	3 (16%)	14 (20%)	0.29
30-day mortality	0	0	1 (5%)	0	0.09

multivariate analysis, Pathological tumor size and WHO 2010 grade were independent predictors of recurrence among parameters that were accessible postoperatively.

All patients with $\leq$10 mm sized tumors ($n = 59$) were disease free at 1-, 3- and 5-year follow-up (Fig. 1b). 10.2% ($n = 5$) of tumors below 10 mm in size presented with presence of biliary or pancreatic duct dilatation on preoperative CT. Patients with tumors sized 11–20 mm ($n = 151$) had worse disease-free survival rates at 1-, 3- and 5-year follow-up being 95.1% (±1.8%), 91.0% (±2.7%), and 87.3% (±4.4%), respectively (Fig. 1c). Here, 7.9% ($n = 12$) of tumors between 11 and 20 mm in size presented with presence of biliary or pancreatic duct dilatation on preoperative CT.

For tumors over 20 mm in size on histopathology ($n = 20$), the 1-, 3- and 5-year disease-free survival rates were 77.8% (±9.8%), 71.8% (±10.7%), and 71.8% (±10.7%), respectively, and 35% of them ($n = 7$) presented with biliary or pancreatic duct dilatation on preoperative CT. Of tumors causing biliary or pancreatic duct dilatation ($n = 23$), 65% ($n = 15$) were WHO 2010 grade 1, 26% ($n = 6$) grade 2, 4% ($n = 1$) grade 3 (grade missing $n = 1$), and 17% ($n = 4$) had metastatic lymph nodes.

Behavior of tumors considered at low-risk of recurrence

Seventy-one patients were considered as low-risk of recurrence based on the following criteria[11]: (i) 2 cm or smaller on preoperative imaging, (ii) no bile or pancreatic duct dilation, (iii) sporadic, (iv) asymptomatic, (v) no lymph node or distant metastasis in imaging studies, and (vi) WHO 2010 grade 1. The 1-, 3- and 5-year disease-free survival rates in this subgroup were 98.6% (±1.4%), 94% (±3.4%), 94% (±3.4%) respectively. One patient died of postoperative complications. Two patients developed disseminated disease, one in the lungs and the other one in liver at 31 and 51 months after surgery, respectively.

Discussion

If surgery used to be the cornerstone of the management of small NF-PNETs, this has been recently challenged. Indeed, in view of the severe and frequent complications of pancreatic surgery and the natural history of sporadic small NF-PNET $\leq$20 mm, expectant management has recently been proposed as a possible option.

In the present European multicentric study, including 210 patients with resected ($\leq$20 mm) small NF-PNETs, several observations were made. First, about 7% of tumors presented with nodal metastasis at the time of resection (11% in patients in whom lymphadenectomy was performed). Second, overall 5-year disease-free survival was excellent (approximately 94%), and most importantly, none of the patients with tumors size below 10 mm recurred. Third, presence of biliary or pancreatic duct dilatation, size on preoperative CT, and WHO 2010 grade were independent predictors of recurrence. The presence of pancreatic duct involvement was identified recently also in another series as poor prognostic factor.[20] Fourth, parenchyma-sparing pancreatectomy carried the highest risk for pancreatic

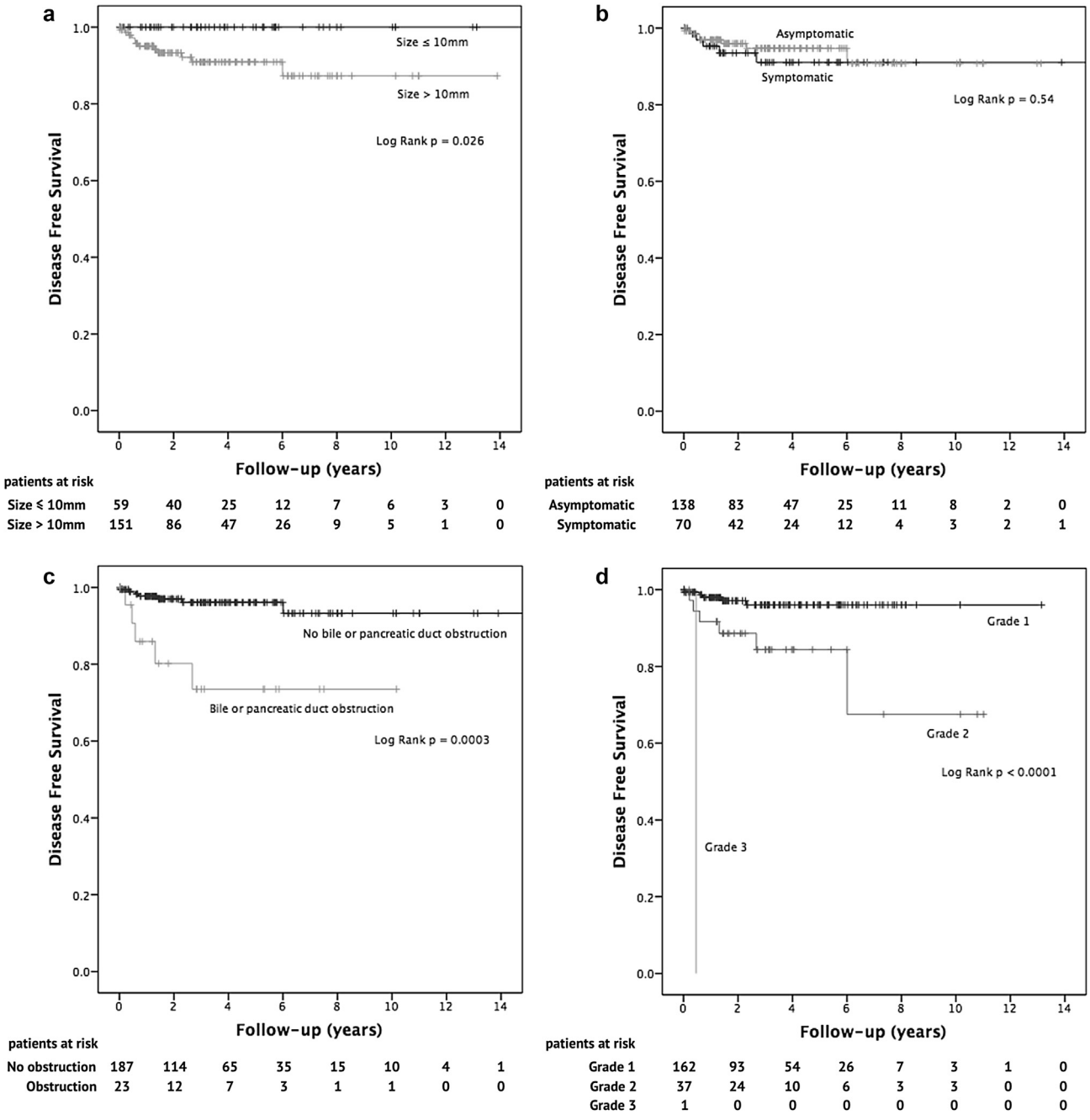

Figure 1 Disease-free survival of patients with sporadic small (≤2 cm) nonfunctional pancreatic neuroendocrine tumor stratified by a) size on preoperative imaging, b) symptoms, c) ductal obstruction status, and d) WHO 2010 grade

fistula, but was associated with long-term disease-free survival similar to formal resection in highly selected patients.

If long-term disease-free survival after curative surgery is excellent, the results of non-operative management are of paramount interest. Two recent systematic reviews have explored the safety and feasibility of a non-operative management for asymptomatic small NF-P-NETs.[8,21] While 22% of sporadic tumors showed growth during follow-up, only 12–14% required resection and no patients developed disseminated disease during the follow-up period.[8,21] On the other hand, 52% of MEN1-related tumors showed growth, 25% underwent surgery and 9% developed disseminated disease, indicating that patients with MEN1-syndrome might need different strategy than patients with sporadic tumors.[8] Taken together, these results favor a wait-

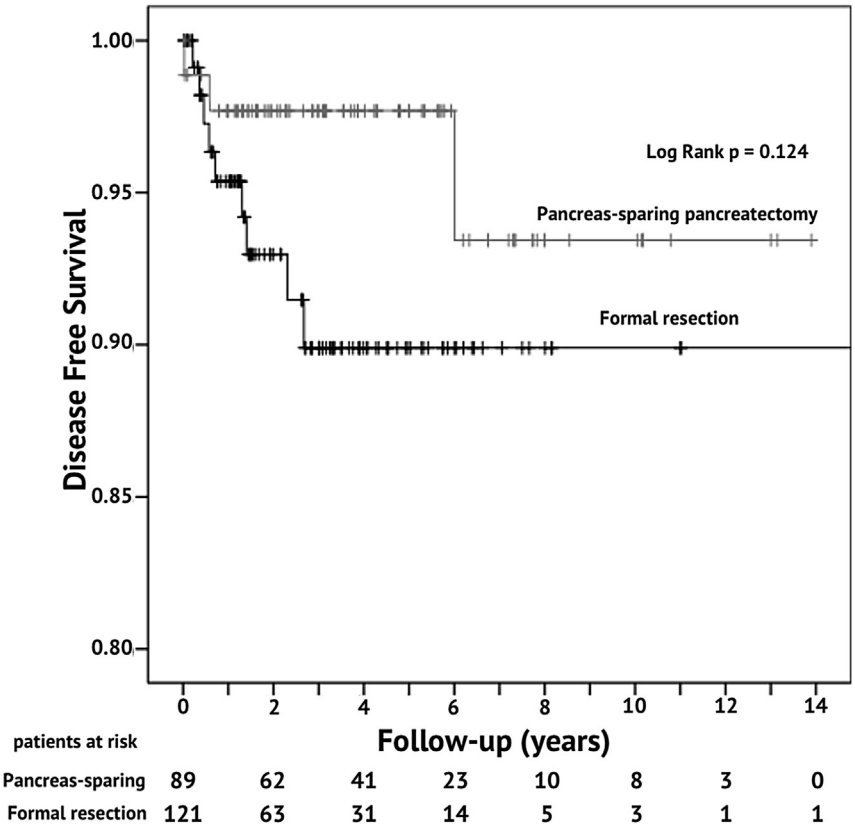

Figure 2 Disease-free survival in patients who underwent pancreas-sparing pancreatectomy compared to formal resection

and-see policy in selected patients with asymptomatic small sporadic NF-PNET without bile or pancreatic duct obstruction.

However, some patients with small NF-PNET most likely benefit from surgery. Several clinical or radiological preoperative factors have been identified earlier to predict poor prognosis of NF-PNET such as distant metastases, primary tumor size over 2 cm, WHO 2010 grade 2 or 3, or presence of radiological signs of node involvement.[9,22,23] But tumors below 2 cm in size remain poorly discriminant. Recently, genetic or transcriptomic markers have been investigated,[24,25] but they are currently not clinically available, and their clinical relevance still needs to be confirmed. In the current study, larger size (even when below 2 cm), bile or pancreatic duct obstruction, and WHO grade 2–3 were identified as independent risk factors for poor disease-free survival even after surgery, suggesting that patients with growing tumor, presence of bile or pancreatic duct dilation, or suspicion/confirmed WHO grade 2–3 are not good candidates for surveillance.

Significant discrepancy between preoperative CT measurement and pathology size should also be noted. In the present experience, in about 10% of the cases in our study the tumor size was underestimated in the preoperative imaging. This discrepancy has been previously reported regarding pancreatic cancer tumors and cystic lesion size.[26,27] While the correlation between tumor size and malignancy in NF-PNET is well demonstrated,[28] other parameters should also be taken into account. Falconi *et al.* showed that nonincidental diagnosis of the tumor is an independent predictor of malignancy at multivariable analysis,[14,28] as well as KI-67 when preoperatively available on FNA.[29] Age obviously plays a role in selecting patients for surgery versus surveillance. Younger patients have lower risk of mortality after surgery and have longer surveillance ahead of them compared to old patients with possible comorbidities and shorter life-expectancy. Tumor location as well plays a role in selecting patients for surgery, and threshold for surgery might be lower in patients with body/tail lesion that do not require pancreaticoduodenoctemy.

At the moment, there are no tools to predict whose tumor will grow, cause ductal dilation, or transform into WHO grade 2–3 tumor in the future. Thus, the dilemma in treating patients with small NF-PNET arises from the morbidity and mortality of pancreatic surgery – the only known curative treatment of these lesions. The mortality of pancreatic surgery varies between 1% and 3% in high-volume centers,[30,31] but increases up to 6–10% when nationwide data is considered.[32,33] Additionally, the morbidity of pancreatic surgery remains high.[34,35] Furthermore, pancreatic fistula rates are higher in non-adenocarcinoma tumors, such as PNETs.[36] Overall, this indicates that the benefit-risk balance of pancreatic resection needs to be carefully weighted. In the present series from several European centers,

Table 4 Univariate and multivariate analysis of prognostic factors for disease-free survival (DFS)

Variable	OR (95% CI)	Univariate analysis *p*-value	OR (95% CI)	Multivariate analysis *p*-value
Preoperatively available parameters				
Age (by year)	1.02 (0.97–1.07)	0.46		
Gender (male)	1.00 (0.32–3.16)	1		
Asymptomatic	0.70 (0.22–2.21)	0.54		
Location in the head	1.56 (0.49–4.93)	0.45		
Size (imaging, by mm)	1.29 (1.06–1.56)	0.01	1.30 (1.11–1.54)	0.002
Bile duct obstruction	6.77 (1.83–25.11)	0.004	12.1 (3.1–48.1)	0.0004
Pancreatic duct obstruction	4.4 (1.20–16.1)	0.027	7.30 (1.81–29.4)	0.005
Suspicion of nodal involvement	2.49 (0.32–19.3)	0.38		
Postoperatively known parameters				
Formal resection	2.70 (0.73–10.02)	0.14		
Complications $\geq$ Clavien-Dindo 3	0.50 (0.07–3.91)	0.51		
R status	0.27 (0.03–2.36)	0.24		
pN1 (vs. pN0 or NX)	4.25 (1.14–15.84)	0.031	0.88 (0.15–5.19)	0.887
Size (histology, by mm)	1.20 (1.09–1.33)	0.0003	1.16 (1.03–1.30)	0.014
Grade WHO 2010	6.86 (2.39–19.67)	0.0003	4.4 (1.36–14.35)	0.013

early results of surgery are nevertheless favorable. The mortality rate is very low (0.5%). 40% of the patients underwent a parenchyma-sparing pancreatectomy, which were associated with higher risk of pancreatic fistula, but excellent long-term disease-free survival rates in highly selected patients. These points suggest that the patients were appropriately selected and that surgeons correctly estimated the risk-benefit balance of their procedure, excluding patients with high-operative risk and attempting to limit the functional consequences of surgery. Whether to proceed with parenchyma-sparing or formal resection is a delicate decision, and in any case needs to be discussed with the patient and preferably made as a shared-decision. Parenchyma-sparing resections have higher morbidity, especially pancreatic fistula, but this morbidity does not transform into mortality in these patients.[37] On the other hand, parenchyma-sparing surgery yields in better long-term exocrine and endocrine function.[37]

In the absence of high level evidence, current European or NCCN guidelines advocate operative strategy for symptomatic patients and tumors of over 2 cm in size,[38,39] but suggest surveillance as an option in smaller sporadic asymptomatic lesions. This strategy is in line with this study's results and also supported by two recent systematic reviews demonstrating the safety of surveillance in selected patients.[8,21] However, selecting patients for surgery versus surveillance needs to be carefully weighted, as demonstrated by two recent large registry based studies[13,15] and a retrospective series[12] that have showed that small asymptomatic NF-PNETs have an unpredictable evolution and that a subset of them can behave malignant. While patient selection can be improved by recommending surgery for patients with bile/pancreatic duct dilation or high KI-67, a few patients will remain having a malignantly behaving tumor. In our material, two out of 71 patients (3%), with tumors consistent with all signs of a benign lesion, developed disseminated disease after surgery. An RCT comparing upfront surgery to surveillance would provide higher level of evidence, but, due to the rarity of the tumors, is unlikely to be carried out in the near future.

These observations also question the carcinogenesis of PNET. Whether a G1–G2 sequence exists as an adenoma-carcinoma sequence for pancreatic adenocarcinoma remain to be formally demonstrated. It is possible that the majority of PNET never become clinically relevant, and that the few patients who would progress can be identified during an initial observation. In this subgroup of patients, which may represent about 15% of small NF-PNET, it seems that delayed surgery would not compromise long-term outcomes.[11] However, earlier identification of progressive tumor would allow prophylactic surgery, and possible parenchyma sparing procedures. In this setting, systematic FNA could be helpful at least in order to rule out, G2 or high-G2 tumor, from a surveillance strategy.

The strength of this study is the relatively large cohort stemming from several pancreatic surgery centers in the Europe, and thus providing better external validity than small single-center cohorts. Large number of patient allowed for multivariate analyses, and the detection of the role of pancreatic and bile duct obstruction on the prognosis of patients with small NF-PNET.

We are, of course, aware of some limitations of the present study. First, it is limited by its retrospective nature with inherited biases, such as the absence of standardized preoperative assessment. Second, we have data only on resected patients, and it is unknown how many patients have been under surveillance during the same time period in the participating centers. This

would be of paramount interest, but unfortunately registries are kept for patients undergoing surgery only. Third, the reason why exactly these patients underwent surgery instead of surveillance is unknown, and might be surgeon and/or patient specific. Finally, the median follow-up in our series was just around 3 years, which might be too short to detect all recurrences.

Further, there was a low proportion of G3 NF-PNETs in our cohort ($n = 1$). Most likely reasons for this are: (i) These tumors usually present with metastases, and metastatic tumors were excluded in our cohort. (ii) These tumors are rapidly growing and thus are often diagnosed beyond 2 cm, and again excluded from our cohort.

In conclusion, the postoperative and long-term outcome in small NF-PNET is excellent for the vast majority of patients. However, in sporadic small NF-PNET, presence of biliary or pancreatic duct dilatation on preoperative CT and WHO grade 2–3 are risk factors for aggressive tumor biology, and these patients, regardless of their tumor size, should undergo formal pancreatic resection with lymphadenectomy. The remaining patients are at low-risk of recurrence and a wait-and-see policy might be considered. As level 1 evidence is difficult, if not impossible, to obtain, other centers are encouraged to report their experience treating small NF-PNETs.

Acknowledgments

This work was performed and written as part of a project of the 7th Pancreas 2000 program funded and organized by the European Pancreatic Club (EPC). We would like to thank Bengt Holmberg for its constant and long-term support. None of the authors have any financial or any other kind of personal conflicts of interest.

Funding

Vatsatautien tutkimussäätiö Foundation and Mary and Georg Ehrnrooth's Foundation provided funding for Ville Sallinen. This work was performed and written as part of a project of the 7th Pancreas 2000 program funded and organized by the European Pancreatic Club (EPC).

Conflicts of interest

None to declare.

References

1. Metz DC, Jensen RT. (2008) Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 135:1469–1492.
2. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV *et al*. (2008) Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 9:61–72.
3. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE *et al*. (2008) One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26:3063–3072.
4. Allen PJ, Gönen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM *et al*. (2014) Pasireotide for postoperative pancreatic fistula. *N Engl J Med* 370:2014–2022.
5. Fong ZV, Ferrone CR, Thayer SP, Wargo JA, Sahora K, Seefeld KJ *et al*. (2014) Understanding hospital readmissions after pancreaticoduodenectomy: can we prevent them?: a 10-year contemporary experience with 1,173 patients at the Massachusetts General Hospital. *J Gastrointest Surg* 18:137–144.
6. He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA *et al*. (2014) 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. *HPB* 16:83–90.
7. Jiang H, Liu N, Zhang M, Lu L, Dou R, Qu L. (2016) A randomized trial on the efficacy of prophylactic active drainage in prevention of complications after pancreaticoduodenectomy. *Scand J Surg* 105:215–222.
8. Sallinen V, Le Large T, Galeev S, Kovalenko Z, Tieftrunk E, Araujo R *et al*. (2017) Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors – a systematic review and meta-analysis. *HPB Oxf* 19:310–320.
9. Sallinen V, Haglund C, Seppänen H. (2015) Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: do size and symptoms matter? *Surgery* 158:1556–1563.
10. Lee LC, Grant CS, Salomao DR, Fletcher JG, Takahashi N, Fidler JL *et al*. (2012) Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. *Surgery* 152:965–974.
11. Gaujoux S, Partelli S, Maire F, D'Onofrio M, Larroque B, Tamburrino D *et al*. (2013) Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 98:4784–4789.
12. Haynes AB, Deshpande V, Ingkakul T, Vagefi PA, Szymonifka J, Thayer SP *et al*. (2011) Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg* 146:534–538.
13. Gratian L, Pura J, Dinan M, Roman S, Reed S, Sosa JA. (2014) Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. *Ann Surg Oncol* 21:3515–3521.
14. Birnbaum DJ, Gaujoux S, Cherif R, Dokmak S, Fuks D, Couvelard A *et al*. (2014) Sporadic nonfunctioning pancreatic neuroendocrine tumors: prognostic significance of incidental diagnosis. *Surgery* 155: 13–21.
15. Sharpe SM, In H, Winchester DJ, Talamonti MS, Baker MS. (2014) Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. *J Gastrointest Surg* 19: 117–123.
16. Falconi M, Plöckinger U, Kwekkeboom DJ, Manfredi R, Körner M, Kvols L *et al*. (2006) Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology* 84:196–211.
17. Dindo D, Demartines N, Clavien P-A. (2004) Classification of surgical complications. *Ann Surg* 240:205–213.
18. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*, 8–13.
19. Bosman FT, Carneiro F, Hruban RH, Theise ND. (2010) *WHO classification of tumours of the digestive system*. Lyon: IARC.
20. Nanno Y, Matsumoto I, Zen Y, Otani K, Uemura J, Toyama H *et al*. (2017) Pancreatic duct involvement in well-differentiated neuroendocrine tumors is an independent poor prognostic factor. *Ann Surg Oncol* 24:1127–1133 [Epub ahead print].
21. Partelli S, Cirocchi R, Crippa S, Cardinali L, Fendrich V, Bartsch DK *et al*. (2017) Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *Br J Surg* 104:34–41.

22. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY *et al*. (2008) Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors. *Ann Surg* 247:490–500.
23. Partelli S, Gaujoux S, Boninsegna L, Cherif R, Crippa S, Couvelard A *et al*. (2013) Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). *JAMA Surg* 148:932–938.
24. Haugvik S-P, Vodák D, Haugom L, Hovig E, Gladhaug IP, Heim S *et al*. (2016) Transcriptomic profiling of tumor aggressiveness in sporadic nonfunctioning pancreatic neuroendocrine neoplasms. *Pancreas* 45: 1196–1203.
25. Marinoni I, Kurrer AS, Vassella E, Dettmer M, Rudolph T, Banz V *et al*. (2014) Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. *Gastroenterology* 146:453–455.
26. Arvold ND, Niemierko A, Mamon HJ, Fernández-del Castillo C, Hong TS. (2011) Pancreatic cancer tumor size on CT scan versus pathologic specimen: implications for radiation treatment planning. *Int J Radiat Oncol Biol Phys* 80:1383–1390.
27. Lee YS, Paik K-H, Kim HW, Lee J-C, Kim J, Hwang J-H. (2015) Comparison of endoscopic ultrasonography, computed tomography, and magnetic resonance imaging for pancreas cystic lesions. *Medicine* 94:e1666.
28. Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P *et al*. (2011) Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery* 150:75–82.
29. Scarpa A, Mantovani W, Capelli P, Beghelli S, Boninsegna L, Bettini R *et al*. (2010) Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol* 23:824–833.
30. Winter JM, Brennan MF, Tang LH, D'Angelica MI, DeMatteo RP, Fong Y *et al*. (2012) Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. *Ann Surg Oncol* 19: 169–175.
31. Cameron JL, He J. (2015) Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 220:530–536.
32. Nimptsch U, Krautz C, Weber GF, Mansky T, Grützmann R. (2016) Nationwide in-hospital mortality following pancreatic surgery in Germany is higher than anticipated. *Ann Surg* 264:1082–1090.
33. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME *et al*. (2007) Perioperative mortality for pancreatectomy: a national perspective. *Ann Surg* 246:246–253.
34. Pecorelli N, Carrara G, De Cobelli F, Cristel G, Damascelli A, Balzano G *et al*. (2016) Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. *Br J Surg* 103: 434–442.
35. Ansari D, Tingstedt B, Lindell G, Keussen I, Andersson R. (2017) Hemorrhage after major pancreatic resection: incidence, risk factors, management, and outcome. *Scand J Surg* 106:47–53.
36. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 216: 1–14.
37. Hüttner FJ, Koessler-Ebs J, Hackert T, Ulrich A, Büchler MW, Diener MK. (2015) Meta-analysis of surgical outcome after enucleation versus standard resection for pancreatic neoplasms. *Br J Surg* 102: 1026–1036.
38. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M *et al*. (2016) ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and nonfunctional pancreatic neuroendocrine tumors. *Neuroendocrinology* 103: 153–171.
39. Oberg K, Knigge U, Kwekkeboom D, Perren A, ESMO Guidelines Working Group. (2012) Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 23. vii124–vii130.